

Prenatal Alcohol Exposure and Metabolic Disorders in Pediatrics

Subjects: **Obstetrics & Gynaecology**

Contributor: Martina Derme , Martina Briante , Mauro Ceccanti , Giuseppe Giannini , Mario Vitali , Marisa Patrizia Messina , Maria Grazia Piccioni , Alessandro Mattia , Simona Nicotera , Alba Crognale

Prenatal alcohol exposure is responsible for increasing chronic disease risk in later life, including obesity and metabolic syndrome. Alcohol drinking may compromise endogenous antioxidant capacity, causing an increase in free radicals and reactive oxygen species in the newborn. Excessive reactive oxygen species could attack the cellular proteins, lipids, and nucleic acids, leading to cellular dysfunction. Moreover, oxidative stress could play a crucial role in the altered synthesis and release of neurotrophins and progressive mitochondrial modifications with uncontrolled apoptosis.

fetal alcohol spectrum disorder (FASD)

prenatal alcohol exposure (PAE)

oxidative stress

metabolic disorders

1. Introduction

Prenatal alcohol exposure (PAE) is the foremost avoidable reason for congenital abnormalities and developmental disabilities and affects 2.4–4.8/1000 children ^[1]. PAE may also raise, in later life, chronic disease risks such as obesity, metabolic syndrome ^[2], and liver disease ^{[3][4]}.

Worldwide, almost 10% of pregnant women drink alcohol. The highest rate of alcoholism during pregnancy is in Europe (25.2%), followed by the American Region (11.2%), the Western Pacific Region (8.6%), the African Region (10.0%), and the South East Asia Region (1.8%). The lowest prevalence is present in the Eastern Mediterranean Region (0.2%) (**Figure 1**) ^[5]. Different Mediterranean studies measuring gestational alcohol drinking in women through the analysis of different ethanol metabolites or in the hair, meconium, or urine data showed high variability with values ranging from 3 to 4% up to more than 30% ^{[6][7][8][9][10][11][12]}.

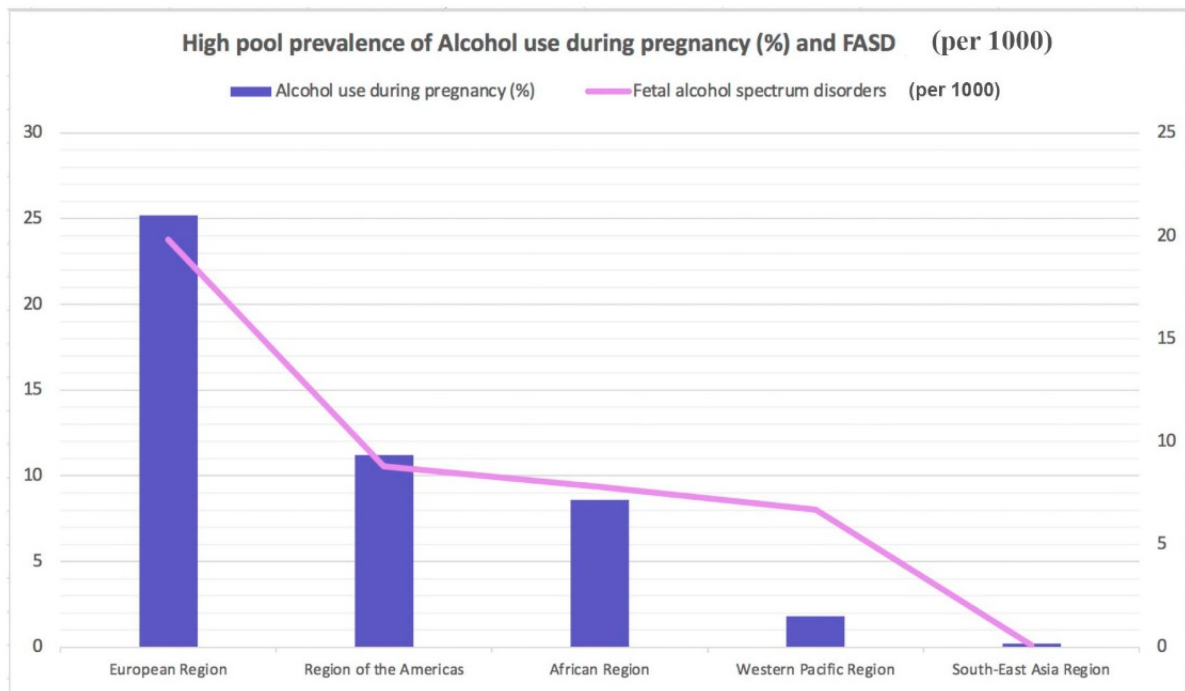


Figure 1. Highest pooled prevalence of alcohol use during pregnancy (%) and fetal alcohol spectrum disorders (per 1000).

Numerous risk factors have been discovered for alcoholism in pregnancy: older age; higher socioeconomic status, salary, and educational levels; smoking; and unintended pregnancy [6][7][13][14].

Fetal alcohol spectrum disorders (FASD) is a “container” word that implies the type of circumstances resulting from PAE. FASD includes disorders such as partial fetal alcohol syndrome (pFAS), fetal alcohol syndrome (FAS), alcohol-related birth defects (ARBD), and alcohol-related neurological developmental disorders (ARND) [15][16][17][18][19][20][21][22][23][24]. Several FASD analytic guidelines have been proposed; among the most recent, Hoyme’s guidelines are quite useful [25]. These guidelines were made by a panel of expert authors who analyzed more than 10,000 children with potential FASD. They elaborated a diagnostic process that requires a multidisciplinary approach and a collaboration between pediatricians, geneticists, maternal-fetal specialists, psychiatrists, speech pathologists, physical therapists, audiologists, and ophthalmologists. The advantage of these guidelines is the possibility of elaborating a diagnosis in the prenatal period.

Oxidative stress seems to play a key role in the pathogenesis of both neuropsychiatric and metabolic disorders in pediatrics [26][27]. Ethanol (EtOH) can alter the endogenous antioxidant ability by depleting the levels of glutathione peroxidase and producing free radicals. Free radicals and reactive oxygen species (ROS), such as hydroxide (HO^-) and superoxide ($\text{O}_2^{\cdot-}$) ions, are derived by O_2 partial reduction. They can affect a cell’s structure by damaging nucleic acids, carbohydrates, proteins, and lipids. These molecules are responsible for inducing uninhibited apoptosis of fetal brain damage in children with FASD [28][29]. The FASD neuropsychiatric effects may be justified by EtOH drinking, inducing the apoptosis of serotonergic neurons, as shown in rodent models [30].

2. Mechanism of Oxidative Stress in Metabolic Disorders

EtOH consumption in pregnancy results in an alteration of oxidative status. A recent case report [31] described increased oxidative stress in a mother abusing ethanol drinking during gestation and in her infant a few days after delivery. The FORT (free oxygen radicals test) was used, indeed, to measure the oxidative stress in the mother and her child [32]. The FORT is a colorimetric assay based on the ability of transition metals such as iron to catalyze, in the presence of hydroperoxides (ROOH), the formation of free radicals (reactions 1–2), which are then entrapped by an amine derivative, CrNH₂. The amine reacts with free radicals, creating a colored, fairly long-lived radical cation, measurable at 505 nm (reaction 3). The color intensity correlates directly to the radical compounds and the hydroperoxide concentrations and, consequently, to the oxidative status of the sample according to the Lambert–Beer law [32]. Values superior to 330 U indicate a situation of progressing oxidative stress.

Oxidase enzymes (Nox), the mitochondria, and nicotinamide adenine dinucleotide phosphate (NADPH) are the two main apparatuses of ROS production inside the cell [33]. The Nox enzymes (Nox1, Nox2, Nox3, Nox4, Nox5, DUOX1, and DUOX2) are cell membrane proteins and Nox2-Nox3 are involved in different pathological circumstances [33]. ROS are produced in the mitochondria during oxidative phosphorylation by converting nicotinamide adenine dinucleotide (NADH) to NAD⁺ [34][35]. The superoxide anion and Nox2 are quickly converted by the superoxide dismutase enzyme into hydrogen peroxide (H₂O₂), an important signaling molecule [36][37]. Indeed, H₂O₂ is a potent oxidizing agent, and based on these considerations, cells are forced to secrete antioxidant peptides that convert H₂O₂ to water, including catalase, peroxiredoxin, thioredoxin, and glutathione (GSH) [35][38]. It is important that H₂O₂ production is equal to its reduction [39].

Pathological diseases such as insulin resistance, obesity, chronic inflammation, hyperglycemia, and dyslipidemia can cause overproduction of ROS [40][41]. The excessive ROS presence may elicit cellular damage, in particular, peroxidizing lipids and altering DNA [42]. Lipid peroxides, lipid peroxidation end products, may be toxic to the cell and should be removed by glutathione throughout a specific mechanism [43]. Indeed, previous investigations revealed that patients metabolically affected by the syndrome displayed greater biomarkers of oxidative damage and lower plasma antioxidant enzyme activity than healthy people [44]. Peroxidation and nitrosylation can alter nuclear acids and proteins [35]. These end products do not typically directly harm the cell [35]. However, the increase in inactive proteins may alter the cell's capability to metabolize them, determining the activation of apoptosis and DNA damage [43]. In addition, such elevation in modified proteins reduces their function, leading to severe impairment of regular cell action [36][43]. The ROS overproduction leads to oxidative stress elevation, which also disrupts redox control and signaling, determining gene expression alteration and increasing stress response elements and growth factors by activating the apoptosis path [39][45]. Furthermore, oxidative stress may elicit profibrotic and proinflammatory pathways, which alter endothelial dysfunction and insulin metabolic signaling by promoting renal and cardiovascular fibrosis [39][46].

3. Oxidative Stress in Pediatrics after Fetal Alcohol Exposure

FASD is an umbrella expression defining all the circumstances resulting from PAE: partial fetal alcohol syndrome (pFAS), fetal alcohol syndrome (FAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) [47].

The vulnerability to ethanol strongly depends on the genetic background of each individual [48], and particularly for gestation, it is not possible to establish a consumption-safe level. Indeed, the only practicable recommendation for pregnant women is to avoid alcohol use completely. Damage due to PAE can be long-lasting with no cure [49], so early management and correct identification may support prevention and alleviate the metabolic and neurological consequences affecting the FASD person later in life. FASD severity depends on the amount and drinking frequency, as well as the gestational age at which the ethanol was assumed by the pregnant woman [50][51]. Intervention services, prevention and sensibilization for the mothers could moderate the FASD incidence [52].

The fetus has inadequate or null aptitudes in alcohol metabolization and removal [53]. Indeed, the several enzymes aimed at ethanol degradation gradually elevate their actions during the various steps of gestation [32].

Figure 2 summarizes the mechanisms through which oxidative stress has a major role in the pathogenesis of neurological and metabolic diseases of patients exposed to alcohol in the prenatal period.

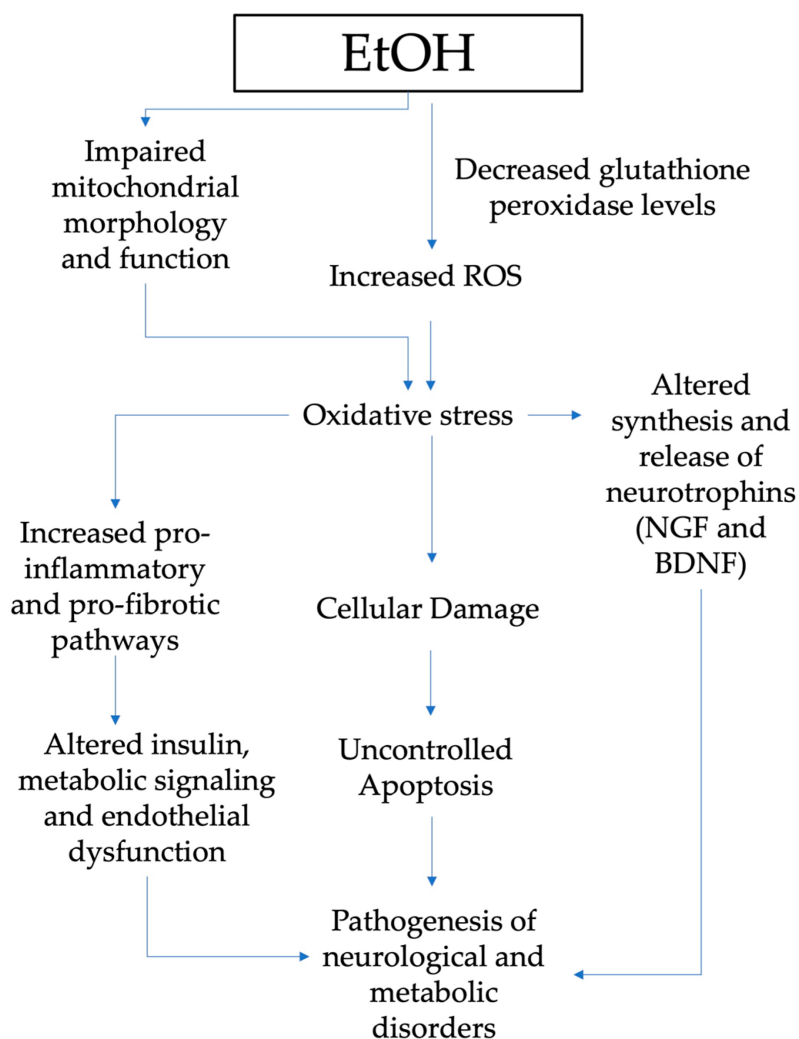


Figure 2. Pathogenesis of neurological and metabolic diseases and role of oxidative stress in patients exposed to alcohol in the prenatal period (EtOH, ethanol; ROS, reactive oxygen species; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor).

EtOH can alter the endogenous antioxidant ability by reducing GSH and generating free radicals, which are considered to be responsible for uncontrolled apoptosis [54][55]. Chronic and acute alcohol drinking during prenatal development also impacts mitochondrial function and morphology, another crucial cell oxidative stress source [56]. Depleted mitochondrial activity is discovered in the early postnatal stage in liver and brain tissues, including the cerebellar brain cells of prenatally exposed rats [56].

Oxidative stress has a key role in the altered synthesis and release of growth factors such as the nerve growth factor—NGF and brain-derived neurotrophic factor—BDNF [57]. Animal model studies disclosed many findings on gestational alcohol exposure's effects on neurotrophins [58][59]. Indeed, maternal alcohol exposure during gestation affects the neurotrophins' brain signaling pathways, as well as in target tissues for ethanol intoxication. NGF and BDNF are peptides that not only play a pivotal role in the development, survival, and function of the central and peripheral nervous systems but also regulate the pathogenesis of other problems induced by alcohol exposure [58][60][61].

The supplementation with natural compounds with antioxidant properties, such as the polyphenols extracted from vegetables, might, of course, counteract the toxic prooxidant effect of alcohol abuse during pregnancy [62][63][64][65][66][67]. Furthermore, a healthy diet during pregnancy containing proper amounts of fresh vegetables containing polyphenols, as evidenced by the Mediterranean diet, might reduce the oxidative stress induced by gestational alcohol drinking [68][69][70][71][72][73][74][75].

4. FASD and Metabolic Disorders

PAE and subsequent FASD can cause lifelong alterations in affected offspring, including a permanent imbalance in metabolic homeostasis. These effects of alcohol consumption during pregnancy could be linked to an increased risk of intrauterine growth restriction (IUGR) [76] due to blood flow impairment [77] and abnormal placentation process [78], with following catch-up growth [79]. This phenomenon is strongly correlated with the development of some features of metabolic syndrome, such as central obesity, glucose intolerance, and dyslipidemia [80].

Several studies conducted both in humans and in animal models try to underline the effects of PAE on metabolism. In 2020, Weeks et al. [81] demonstrated, with a retrospective cross-sectional study in adults with any form of FASD diagnosis, that alcohol exposure in utero increases the incidence of hypertriglyceridemia, type 2 diabetes mellitus, and lower HDL cholesterol, independently of BMI in the case of the male cohort. Female patients had, instead, an increased risk of being overweight and obese. They confirmed these data with zebrafish, a particularly suitable model considering its flexibility and anatomical similarities to humans, the presence of many evolutionary conserved pathways, and the simplicity of alcohol administration in an aqueous environment [82].

The relationship between PAE and HFD was also analyzed by Shen and colleagues [83] in 2014 when they evaluated the susceptibility of female adult offspring to HFD-induced nonalcoholic fatty liver disease (NAFLD), which is considered a liver indicator of metabolic syndrome [84]. In the group exposed to PAE and HFD, they found a decrease in serum corticosterone and an increase in serum IGF-1, glucose, and triglyceride with notable catch-up growth, higher metabolic status, and NAFLD formation. The authors suggest a “two-programming” hypothesis for the augmented risk of NAFLD in the case of prenatal alcohol exposure, in which the “first programming” consists of the intrauterine programming of liver glucose and lipid metabolic function and the “second programming” is led by postnatal adaptive catch-up growth triggered by intrauterine programming of glucocorticoid-IGF1 axis.

5. FASD and Cardiovascular Disease

Congenital heart defects (CHDs) are the most common congenital anomaly, with a worldwide prevalence of 9.1 in 1000 live births [85][86]. The etiology of CHDs is still unknown; most of them are due to genetic anomalies and aneuploidies. The Maternal Heart Association established that prenatal exposure to therapeutic drugs and substances of abuse, like alcohol and cigarettes, are important risk factors [87]. PAE has also been shown to be related to the occurrence of CHDs. Alcohol has severe effects on the cardiovascular system, leading to various disease states such as arrhythmias [88] and dilated cardiomyopathy [89].

The cardiotoxicity of alcohol does not interest only adult consumers. According to the Centers for Disease Control and Prevention (CDCP), about 10% of pregnant women mentioned drinking fluently, and approximately 50% of them mentioned binge drinking, which increases the risk of FASD [90]. The proportion of children with CHDs among children with FASD is almost 67% [91]. The molecular mechanisms can explain the illness, but the American teratogenic effects of PAE are still poorly understood because of the complexity of alcohol effects and the correlation with timing, amount, and duration of exposure, as well as genetic susceptibility [92].

By modeling chronic alcohol exposure-induced cardiotoxicity in hiPSC-CMs, they showed that EtOH causes decreased mitochondrial membrane potential and mitochondrial content, decreased mitochondrial function, and altered expression of related genes [93]. EtOH also modified the glycolytic process and carbohydrate metabolic process as well as a reply to hypoxia, increased glycolysis, decreased mitochondrial function, and increased oxidative stress [93]. Therefore, an upregulation of T-cell chemotaxis has been shown as a potential causal link to proinflammatory response [93]. Further studies are needed to better understand the mechanisms of alcohol cardiotoxicity and teratogenicity in order to prevent the dramatic effect of PAE on the offspring of mothers consuming alcohol.

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